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(71) Applicant
Aktiebolaget Leo,
(Sweden),
Norrbroplatsen 2,
S-251 09 Helsingborg,
Sweden.
(72) Inventors
Ove Birger Ferno,
Stig Karl Artur Helgertz,
Corfitz Bengt Ingvar
Ohlsson.
(74) Agent and/or Address for
Service
Gill, Jennings & Every,
53/64 Chancery Lane,
London WC2A 1HN.

(54) **Smoking substitutes for nasal administration**

(57) An aqueous composition having a viscosity of at least 100 cp and a pH of from 2 to 6, contains 0.5 to 10% w/v, calculated as a free base, of nicotine or a physiologically-acceptable acid addition salt thereof. Such a composition can be administered into a nostril, and can reduce tobacco-dependence.

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Fig. 1.

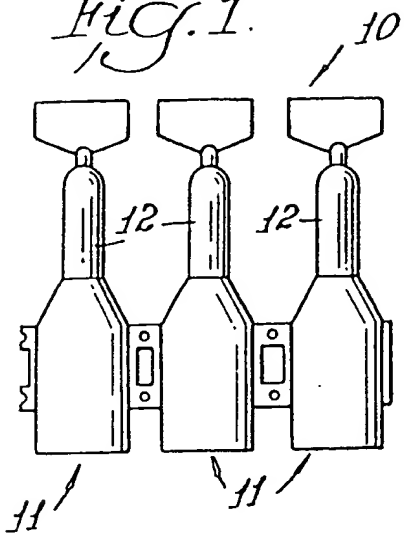


Fig. 3.

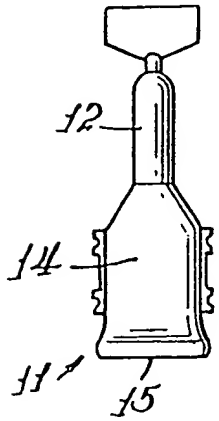


Fig. 4.

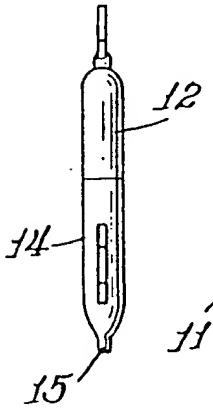


Fig. 5.

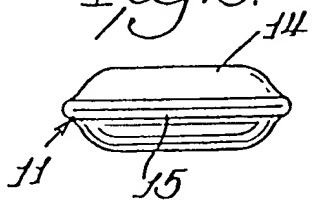


Fig. 2.

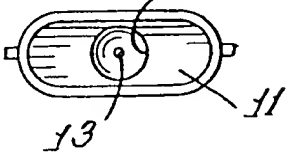


Fig. 6.

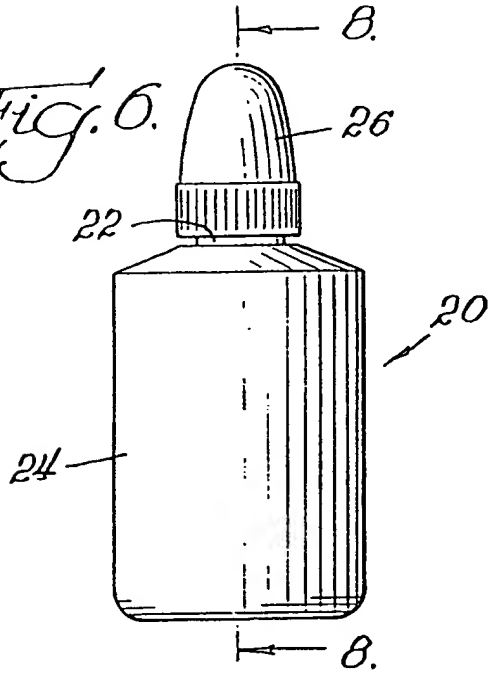


Fig. 7.

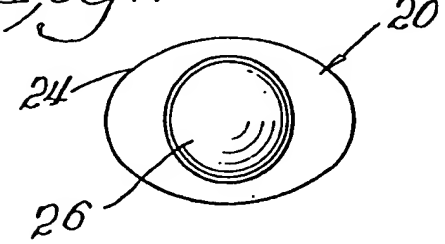


Fig. 8.

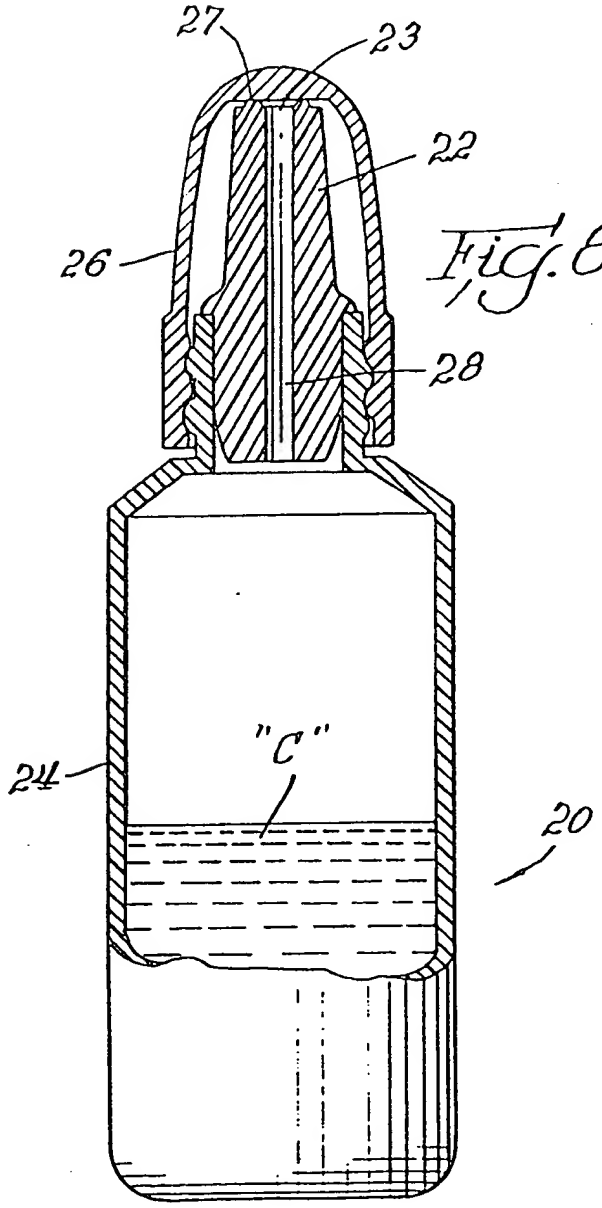


Fig. 9.

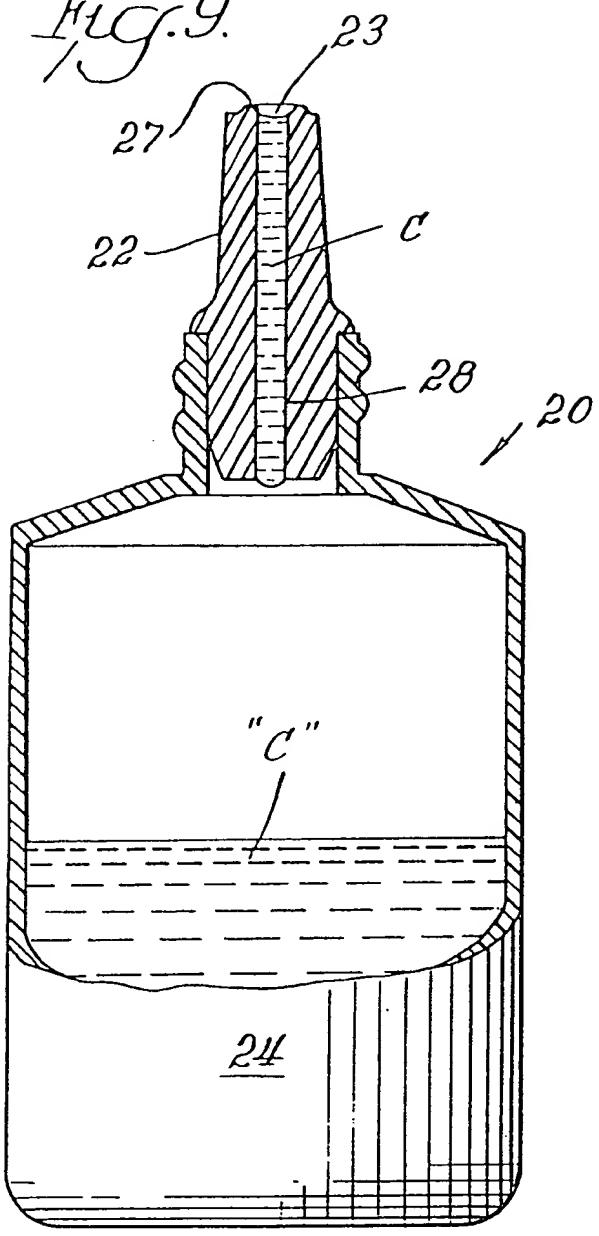


Fig. 10.

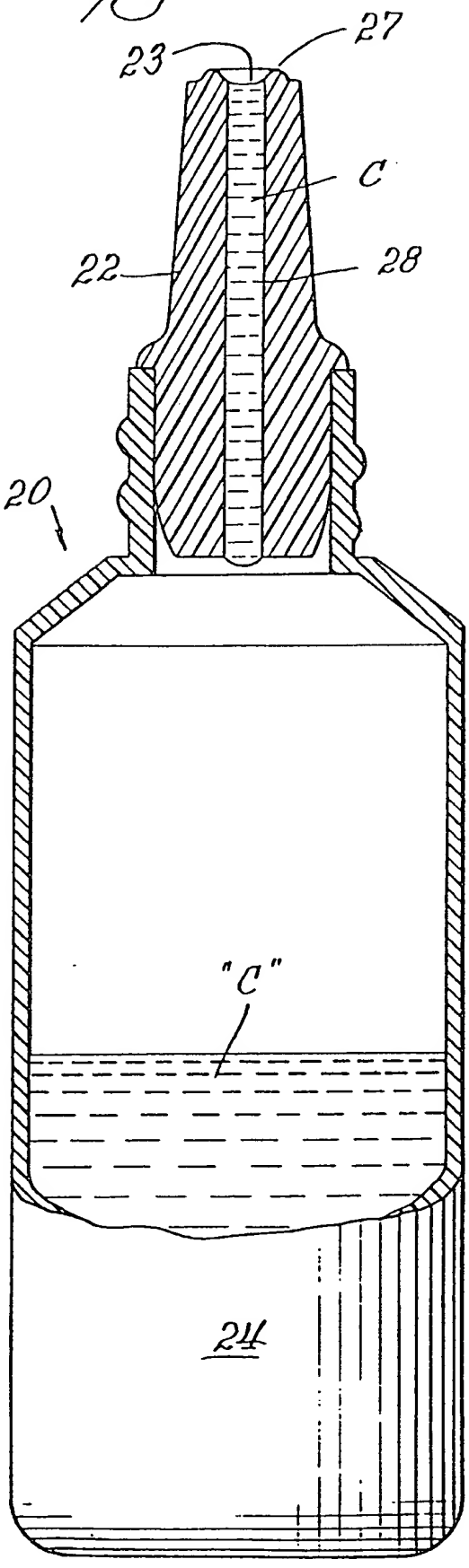
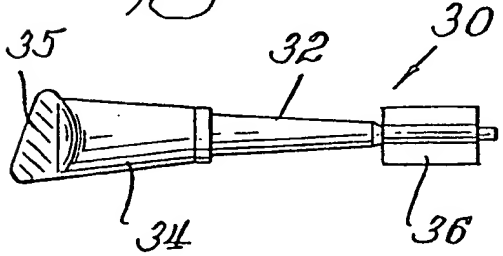


Fig. 11.



SPECIFICATION

Smoking substitutes for nasal administration

It is now widely recognied that smoking can be a major health hazard. This hazard can be reduced by reducing or eliminating smoking, but smokers find this extremely difficult, and it is generally accepted that this difficulty is caused by nicotine-dependence. While the presence of nicotine in tobacco smoke is considered to be a major risk factor, there are other, more important risk factors in the substances formed during the combustion of tobacco, such as carbon monoxide, tar products, aldehydes and hydrocyanic acid.

It has therefore been proposed that nicotine should be provided in a form or manner other than by smoking. For example, chewing tobacco and snuff (taken nasally or orally) are known, but are not without harmful effects. Nicotine-containing chewing gums are known, as disclosed in US-A-3877468, US-A-3901248 and US-A-3845217, comprising a nicotine-containing cation-exchange resin complex in a gum base, preferably together with a buffer which maintains the pH of the saliva above its normal physiological value. Nicotine-containing chewing gum is not generally acceptable to hardened smokers or to smokers with dentures.

Herxheimer *et al.*, Lancet (1967) II 754-5, suggest, and GB-A-1528391 and BG-A-2030862 disclose, aerosol compositions, adapted to be sprayed into the mouth. It is doubtful that spraying can be as effective as chewing gum.

US-A-3870794 suggest compositions of nicotine for treating certain emotional disorders.

DE-A-2313996 describes certain water-soluble readily-absorbed snuff powders. These comprise only tobacco aroma extracts and solid, water-soluble absorbents. Such snuff substitutes may apparently be less prone to discolour teeth and fingers than snuff itself.

Although it is increasingly less socially-acceptable, and generally considered non-hygienic, snuff is a form of tobacco, and therefore of nicotine, which is administered nasally. In snuff, nicotine is embodied in a matrix of tobacco, from which it is released slowly, on contact with the nasal mucosa. The resultant absorption of nicotine into the blood is sufficiently slow that finely-ground snuff tobacco is often mixed with additives, including substances such as potash or lime, to increase the pH and rate of absorption. Nicotine itself has both strong taste and smell, and would be unacceptable for general use even without taking into consideration the considerably faster absorption than from snuff.

According to the present invention, an aqueous composition having a viscosity of at least 100 cp and a pH of from 2 to 6, contains 0.5 to 10% w/v, calculated as the free base, of nicotine or a physiologically-acceptable acid addition salt thereof. Such a composition is of utility for nasal administration, as a smoking substitute which can be used to reduce or break tobacco-dependence.

The invention will be generally described with reference to the use of compositions of the invention as smoking substitutes and in forms suitable for nasal administration, i.e. in which all components are acceptable in nasal administration.

A composition of the invention may be in a form of a unit dosage, i.e. a discrete form, which delivers 0.5 to 5, preferably 1 to 4, mg nicotine.

The viscosity of a composition of the invention is preferably at least 1000, and more preferably 3000 to 4000, cp. The preferrred maximum viscosity is 6000 cp.

A unit dosage of the invention may comprise from 0.05 of the aqueous nicotine solution. The volume may be up to 0.5, e.g. 0.1 to 0.3, ml.

The pH of the composition is preferably from 3 to 5. The composition preferably includes a buffer which maintains the pH in the given range, and preferably at from 4 to 6. The composition preferably comprises from 1 to 5, and more preferably from 2 to 4, % w/v of nicotine.

In order to achieve the desired viscosity, a composition of the invention may comprise a thickening agent which is a natural, semi-synthetic or synthetic polymer, or an oil constituting the oil phase of an emulsion. Other preferred ingredients are any or all of emulsifying agents, preservatives, flavours and anti-oxidants.

A composition of the invention may be provided in unit dosage form in a container, e.g. of a plastics material, having an emission aperture in a neck which can be inserted into a nostril, and a relatively large volume chamber to which pressure can be applied to cause emission. Again, a composition of the invention may be provided in a squeeze bottle having a neck, and in either case, the amount emitted from the neck can be adapted to be an individual dosage. In providing compositions of the invention in such containers, the presence of an anti-oxidant is particularly desirable.

Containers from which compositions of the invention can be dispensed are illustrated in the accompanying drawings, in which:

Figures 1 and *2* are plan and bottom views of a container which may be prepared in multiples from a plastic-moulding process, with open ends;

Figures 3, 4 and *5* are respectively plan, side and end views of a closed, filled container;

Figures 6, 7 and *8* are respectively plan, top and side (partially in section along the line 8-8 of Figure 6) of a container having a neck adapted to deliver a single dosage of a composition of the invention, having a cap in place;

Figures 9 and *10* are respectiv ly front and side views, partially in section, of the container of Figure 6 with the cap removed; and

Figure 11 is a plan view of a further type of container which can be used to dispense compositions of the invention.

In referring to the drawings, it should be noted that the same numerals are used for the same parts in Figures 1 and 2, the same numbers plus 10 are used for the same parts in Figures 3, 4 and 5, the same numerals plus a further 10 are used in Figures 6 to 10, and the same numerals plus a further 10 are used to illustrate the same parts in Figure 11. In particular, Figure 1 shows a number of multiply-moulded containers 10 having open ends 11 and necks 12. Figure 2 also illustrates an emission aperture 13. Figures 3, 4 and 5 show similar containers having a pressure chamber 14 and a seal 15 (made, for example, by heat and pressure).

The container 20 illustrated in Figure 6 has a neck 22, a pressure chamber 24 and a cap 26. Figure 8 additionally illustrates a composition "C" in the pressure chamber, an emission aperture 23, a raised rib 27 for sealing against the side of the cap 26, and a passage 28 whose volume is that of a unit dosage. The presence of composition in this passage is illustrated in Figures 9 and 10.

A container of the type illustrated in Figure 1 may be of a material such as polyethylene, polypropylene or polystyrene. It may be multiply-produced and then separated. A composition of the invention is introduced through the bottom end which is then closed by the application of heat and pressure.

It is desirable that the neck portion of the container should have a volume corresponding to a unit dosage. Especially when the composition has low viscosity, the passageway between the pressure chamber and the neck is preferably partially obstructed by a bead or ring, or a series of inwardly-extending protuberances or fingers, usually located at the juncture between the pressure chamber and the neck.

The neck of a container as illustrated in Figure 6 can be filled with a unit dosage of composition by tipping the container to bring the composition in the pressure chamber into contact with the neck, where it is retained when the container is returned to the upright position. Pressure causes emission of a unit dosage.

If the composition has a high viscosity, it is advantageous to include a small capillary or hole in a cap, just above the emission aperture, in order to allow a single squeeze to fill the neck, before removal of the cap and administration into the nostril.

Without wishing to be bound by theory, e.g. on the physiological tolerance to the composition of a subject on whom it is employed, it is believed that maintenance of the prescribed pH-range according to the invention provides the nicotine ion in the form of a salt thereof, rather than in the form of the free base, which at normal physiological pH's of 7 or thereabouts is intolerable on administration to the mucous membrane. At a pH of 7 or above, more than 10% of the nicotine content is in the form of the free base, and absorption is so rapid that untoward physiological effects are observed, frequently of a serious nature. Strong local sensation, such as burning, intensive sneezing, and the like, are often experienced. However, with maintenance of the pH-ranges according to the invention, i.e., about 2-6, untoward sensations and physiological reactions are infrequently encountered, and are of a much less aggravating nature. This is believed to be due to the fact that the absorption of nicotine into the system in the protonated form, i.e., as its salt, occurs much more slowly than when the nicotine is in the unprotonated form, i.e., as the free base. According to this theory of the invention, the physiological pH of the mucous membrane results in a conversion of the salt to the free base at a slow rate, so that excessive amounts are not present in contact with the nasal mucosa. As the salt is slowly converted to the free base by the physiological pH of the nasal mucosa, small amounts which can be tolerated by the subject are made available for absorption. Accordingly, maintenance of the pH-ranges in the aqueous nicotine compositions of the invention within the prescribed ranges is critical and is of the essence of the invention.

In general, then, the present invention involves aqueous nicotine compositions which are suitable for administration directly to the nasal mucosa of the subject, and a method of administering nicotine to a subject as a substitute for smoking comprising the step of applying directly to the nasal mucosa in the nasal cavity such a physiologically-acceptable aqueous nicotine composition as just described.

According to the broader principles of the invention, the volume of the composition in a unit-dose should consist essentially of 0.05 up to 0.5 ml of the aqueous solution of nicotine or physiologically-acceptable acid addition salt thereof, the pH-value should be between 2 and 6, and the composition should contain 10% down to about 0.5% weight per volume of nicotine calculated as the free base, and the viscosity of the composition should be not less than about 100 cp. This viscosity can be conveniently obtained by the employment of physiologically- and nasally-acceptable thickening agents, as will be discussed further hereinafter. Single dose units according to the invention should deliver about 0.5-5 mg of nicotine per unit-dose, and this is a simple relationship readily effected between the concentration of the nicotine solution and the amount administered, as will be readily apparent to one skilled in the art.

By way of further explanation, at a pH of about 6, only about 1% of the nicotine is in th free base form, whereas the remainder of the nicotine is in the form of nicotinium ion, i.e., in the form of a salt with whatever acid may be employed to effect the prescribed pH-range of the composition of the invention. As the pH is decr ased, even less of the nicotine is in the form of the free base, substantially all of the nicotine being in the form of nicotinium ions at the lower pH values. According to the Merck Index, 9th ed., the pH of an 0.05 molar solution of nicotine is 10.2. Thus, nicotine free base is indeed a base and, without adjustment of pH, a solution of free basic nicotine is not only outside the scope of the invention but also unsuitable for use according to the present invention.

According to the invention, either natural or sythetic nicotine may be employed, or a pharmacologically-

acceptable salt thereof. Natural nicotine, as it exists in tobacco, is preferred. Pharmacologically-acceptable salts include, for example, nicotine hydrogen tartrate, nicotine tartrate, nicotine hydrochloride, nicotine dihydrochloride, nicotine sulphate, and so forth. Many such salts are known.

Further, according to the invention, an acid pH is maintained in the compositions of the invention. For maintenance of a pH within the prescribed range, in addition to buffers which may be employed as further disclosed hereinafter, the employment of an acid, preferably an acid of the type just mentioned or citric acid, lactic acid, succinic acid, phosphoric acid, or similar pharmacologically-acceptable acids, for salt formation with the nicotine, may be employed. When the salt itself is not properly within the pH-range, modification may be effected in the usual manner by employment of an acid, a base, or a buffer.

With respect to the volume of solution employed in unit-dose form, it should go without saying that this volume should be sufficient to enter the nasal cavity and maintain contact with the nasal mucosa for a period sufficient for absorption thereof into the bloodstream of the subject, but should not be of such an amount that excessive run-off occurs. Obviously, the amount should not be so great that substantial quantities of the solution run down into the throat of the user, since this is not the object of the invention and untoward side-effects and diminished tolerability always result upon exposure of the buccal cavity to the compositions of the invention. Accordingly, it is not desired that the compositions enter into contact with the buccal cavity and the volume of the composition employed in a unit-dose, and in a unit-dose treatment of a subject, according to this invention should be such that contact with the buccal cavity does not occur.

Moreover, the amount of nicotine in the solution should not vary substantially from the defined 10-0.5 weight/volume per cent of nicotine. The per cent weight/volume of nicotine has been stated as being between 10-0.5, on a diminishing scale, in contrast to the statement of the volume in an ascending order, i.e., 0.05 up to 0.5 ml, to emphasize the fact that an objective is to obtain an effective amount of nicotine per unit-dose, i.e., between 0.5 and 5 mg, preferably 1-4 mg, of nicotine per unit-dose. This is readily accomplished by employing a selected volume and a relative weight/volume concentration of nicotine, as will of course be readily appreciated by one skilled in the art.

Buffer and viscosity aspects of the present invention will be further considered hereinafter.

It should be apparent that the combination of the volume of the composition and the concentration of nicotine in the composition provide the desired unit dosage of nicotine, which is according to the invention between about 0.5 to 5 mg per unit dose. In providing such dosages, it is a simple matter to calculate volume and concentration to end up with a dosage within the desired range. However, from a practical standpoint, it is frequently the case that all of a composition in a particular container, especially in a unit-dose container, is not ejected from the container, upon use. In such case, compensation must be made by employment of increased volume so as to permit ejection and utilization of sufficient volume to provide a dose within the desired range. In point of fact, it has been found that, with a composition of the invention, depending on the viscosity involved, a considerable amount frequently does adhere to the inside of a unit-dose container and remains therein upon use and application. For this reason, it is frequently necessary to compensate by increasing the volume of the composition employed. Depending upon the nature and configuration of the unit-dose container involved, an increase in the volume of the composition in the container by as much as 200%, to ensure the desired dosage upon administration, has frequently been found desirable.

Such a situation is, of course, more pronounced at the lower volume ranges than at the higher volume ranges, since the amount dispensed from a particular container is as usual related to the amount of material in the container. Although excess volume is therefore recommended, to provide the desired dosage upon administration, it is pointed out that an excessively large dose of nicotine is definitely not recommended, so that the volume and the concentration are to be correlated with the amount dispensed in a unit-dose or from a disposable unit in order to provide a nicotine dosage within the prescribed range. Such relationships are simple calculations for one skilled in the art and acquainted with the normal correlations involved in the dispensation of compositions from unit- or multiple-dose containers.

It is to be noted that, according to previous investigators, who were concerned with the rapid absorption of nicotine in the buccal cavity, the solution of the nicotine should have an alkaline pH (A. H. Beckett et al, Journal of Pharmacy and Pharmacology *24*: 115-120, 1972). Quite to the contrary of these investigators, our finding is that the pH of the compositions of the invention for our purpose must be maintained at relatively low pH-ranges, for reasons already stated, but also to avoid the extremely strong and disagreeable taste reactions which occur when the pH is even weakly alkaline.

Accordingly, the present invention provides a novel approach to a smoking substitute which is both socially-acceptable and quite unpredictably not only well-tolerated by the individual, but which also gives a satisfactory absorption, producing blood levels which are in fact similar to those obtained after cigarette smoking, so that a sense of nicotine satisfaction is obtained by a user who requires the same.

Viscosity

As will be noted, the compositions, i.e., the nicotine solutions of the invention, should have a viscosity not less than 100 cp. The reason for this viscosity requirement is so that the solution will adhere to the mucous membrane after introduction into the nasal cavity and will not produce excessive run-off through the nostril or, conversely, as already explained, into th buccal cavity. The necessary viscosity of 100 cp or abov is readily obtained in numerous ways which will be readily understood by one skilled in the art. For example, physiologically- r nasally-acceptable thickening agents may be employed. These may be in the form of th

usual thickening agents, or they may be in the form of the oil phase of an emulsion. Practically all the nicotine will remain in the aqueous phase of an emulsion, whether an oil-in-water or a water-in-oil emulsion is employed for purposes of obtaining the necessary viscosity.

Among the numerous thickening agents which are available in the art and nasally-acceptable may be mentioned the natural, semi-synthetic or synthetic polymers, examples of which are gum arabic, cellulose, methyl cellulose, and poly (ethylene oxide). Mixtures of such polymers may be employed if desired. Further representative thickening agents may be hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, or the like. Sodium and other salts of carboxymethylcellulose can also be used. Microcrystalline cellulose, which is practically insoluble in water, may be used to form a suspension. In contrast, the previously mentioned cellulose derivatives are soluble in water. Additional thickening agents may include polyvinylpyrrolidone, polyethylene glycol, and the like. Whether the thickening agent is a natural, a semi-synthetic, or a synthetic polymer, or a thickening agent of another type, it is only necessary that it be physiologically- and nasally-tolerable and that it be stable within the pH-ranges involved for the composition according to the present invention.

If an emulsion is employed for thickening purposes, as previously stated, this may be either an oil-in-water (o/w) or a water-in-oil (w/o) type. The oil phase of the emulsion may be any suitable mineral, animal, or vegetable oil, including, for example, paraffins, petrolatum, lanolin, beeswax, peanut oil, olive oil, castor oil, or the like. Innumerable oils and other materials which may constitute the oil phase of any particular emulsion are known in the art, and any of these may be employed with facility so long as they are physiologically- and nasally-acceptable and stable within the pH-ranges employed for the compositions of the present invention.

When emulsification is employed as the means of thickening a composition of the invention, an emulsifying agent is employed to advantage. When an emulsifying agent is employed, any emulsifying agent which is stable within the pH-ranges of the compositions of the invention and physiologically- and nasally-acceptable may be employed. In addition, emulsification may be employed as a means of thickening the compositions of the invention together with a thickening agent, which may be used in the water phase of such an emulsion. In such case, the foregoing named thickening agents may be employed for such purpose.

When an emulsifying agent is employed, it may be, for example, cholesterol, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sodium stearate, sodium lauryl sulphate, and the like. Emulsifying agents of any type may be employed, but the non-ionic emulsifyers are preferred to the cationic and anionic types. Amphoteric emulsifying agents, such as lecithin, may also be used.

When thickening agents are employed and, whether they be normal thickening agents or whether the thickening be effected by emulsification, normal procedure in the art is employed. No particular problems are encounterd. As stated in the foregoing, the viscosity of the compositions of the invention should be such as to maintain the composition, upon administration to the nasal passageway, in contact with the nasal mucosa for a sufficient period to permit absorption of the nicotine through the nasal mucosa into the bloodstream of the subject. For this purpose, the amount of the thickening agent, whatever type might be employed, should be such as to render the composition of sufficient viscosity so that it does not suffer from excessive run-off or deposit itself disadvantageously in the buccal cavity through the rear of the nasal passageway. From the standpoint of numerical values, the amount of thickening agent employed should be such as provides a viscosity not less than 100 cp, preferably not less than about 1000 cp, and preferably about 3000-4000 cp. At higher viscosities, as indicated previously and with particular reference to the drawings, the composition of the invention is advantageously dispensed in a unit-dose container or multi-dose container having a unit-dose neck and, upon placement into the container, maintains its position in the neck of the container until use. This is particularly advantageous inasmuch as it permits administration of a unit-dose into the nasal passageway in a convenient manner, and the viscosity of the composition thus not only maintains it in contact with the nasal mucosa for a sufficient period for absorption to occur, but also enables it to be conveniently delivered through the unit-dose container employed or by a corresponding multi-dose container having a unit-dose neck.

Buffering Agents

As already stated, at lower pH's the absorption of nicotine is relatively slow. The time it takes to increase the pH by the action of the normal physiological pH of the nasal mucosa, can be further prolonged by the employment of buffering agents in the nicotine solution. This is not always necessary, especially when the solution originally has a relatively low pH, i.e., a pH in the lower ranges specified according to the invention, for example 2-5. As already stated, the preferred pH-range is 3-5, and buffers which provide effective buffering effect within the range of 2-6 and preferably 4-6 are accordingly preferred. As will be readily understood, the presence of a buffer is more advantageous and desirable when the initial pH of the composition is relatively high in the acceptable range, for the reason that it is not desirable t have the solution pH climb too quickly by virtu of the action of the nasal mucosa into a more basic range, wher tolerance is seriously reduced and untoward sensations are aggravated.

At th other end of the range, of course, for example at a pH of 4, where only about 0.01% of the nicotine is in the unprotonated absorbabl form, and the other 99.9% exists as protonated nicotinium cations, the presence of a buffer is somewhat less important.

With respect to the buffer, when employed it is usually employed in an amount below about 5% by weight,

most preferably between about 0.5 and 3% by weight, although in certain circumstances the amount of the buffer can even be higher, for example up to about 10% by weight.

As far as the physiologically- and nasally-acceptable buffering substances are concerned, numerous are available in the art and any of these may be employed. For example, inorganic water-soluble phosphates are particularly well adapted for use in the compositions of the invention. Other buffering agents which may be employed with equal facility include citric acid, malic acid, lactic acid, succinic acid, tartaric acid, as mixtures with their water-soluble salts. Innumerable other buffering substances which are physiologically- and nasally-acceptable are known in the art, and these may also be employed if desired.

Flavouring

If desired, the composition of the invention may also include a flavouring agent. This may be of any desired kind or type as long as it is physiologically- and nasally-acceptable and compatible with the other ingredients of the composition at the pH-ranges employed. Menthol is a particularly preferred flavouring agent, but numerous others may be employed, such as the usual essential oils, including oil of wintergreen, oil of peppermint, oil of clove, or oil of spearmint, or honey, figs, liquorice, vanilla, or the like.

When no flavouring agent is added, the composition of the invention is characterized by a slight nicotine odour, due to the non-ionized nicotine which, as previously indicated, will vary considerably from the lower to the higher pH-ranges involved in the composition of the invention.

Preservatives

A preservative may also optionally be present in the composition of the invention, and may be of any suitable type, provided only that it is physiologically- and nasally-acceptable and stable within the pH-ranges of the composition of the invention. The presence of a preservative is particularly advantageous when the pH of the solution is above about 4. Representative suitable preservatives include alkylparabens such as methyl paraben and propylparaben, benzoic acid, sorbic acid, chlorocresol, chlorohexidine, or the like. When a preservative is employed, it is generally employed in normal amounts, usually in the range between about 0.01 and 1.0%, generally on the order of 0.1% by weight.

Antioxidants

The composition of the invention may also contain an antioxidant which is compatible with the other ingredients and which is physiologically- and nasally-acceptable and stable under the pH conditions involved. Representative antioxidants include, among others, ascorbic acid, sodium bisulfite, butylated hydroxyanisole, butylated hydroxytoluenes, and the like. A considerable number of antioxidants have found wide use in foods, and any of the extablished antioxidants meeting the requirements as stated in the foregoing may be employed. When an antioxidant is employed in a composition of the invention, it is usually employed in an amount between about 0.001 and 1.0%, generally on the order of 0.01 to 0.1% by weight.

Innumerable flavourings, preservatives, and antioxidants are well known in the art, both in the pharmaceutical and in the food industry, and any of these type materials meeting the prescribed requirements of physiological acceptability and stability under the pH-ranges of the composition of the invention and being compatible with the other ingredients may be employed with facility.

Detailed Description of the Invention

In the following examples the nicotine use is pure natural nicotine base of a salt thereof. The water used can be distilled or deionized. The viscosity of the solutions and emulsions is determined at room temperature with a rotational viscometer, Brookfield LVT, and is given in cp (centipoise) at 12 r. p. m. The volume of the final solution dispensed in the disposable unit-dose containers is calculated to give the dose of nicotine as mentioned in the example. In the multiple-dose containers the neck-portion is such that the dose of nicotine given is the one mentioned in the examples. The total volume of solution dispensed in the multiple-dose containers is about two thirds of its volume.

The following Preparations and Examples are given by way of illustration only, and are not to be construed as limiting.

Example 1

Nicotine	10 g
Sodium dihydrogen phosphate NaH_2PO_4, H_2O	10 g
Hydroxypropyl methylcellulose (Methocel E4M, TM)	20 g
Hydrochloric acid ad pH 4	
Water to make	1000 ml

The nicotine is dissolved in 500 ml of water together with the phosphate which is acting as a buffer. Th pH is adjusted with a 5N HCl-solution.

The hydroxypropyl methylcellulose is dispersed in 300 ml of water at about 60°C.

The nicotine solution is added with stirring to the warm cellulose slurry, the mixture is allowed to cool, and the volume is made up with water to 1000 ml. The viscosity of the solution is found to be about 3900 cp.

The solution is dispensed in disposable single dose units or multiple-dose containers, which deliver a given dose of either 1 mg or 0,5 mg nicotine.

Example 2

The procedure set forth in Example 1 is followed, but the amount of nicotine is replaced by 40 g, the amount of phosphate by 20 g and the pH is adjusted to 6.

To the composition is added menthol 80 mg as a flavouring agent, ascorbic acid 1 g as an antioxidant and methyl para-hydroxybenzoate 1 g as a preservative.

The viscosity is found to be about 3800 cp. The solution is dispensed as in Example 1 so that the given dose is either 4 mg or 2 mg nicotine.

Example 3

The procedure set forth in Example 1 is followed, but the amount of nicotine is replace by 50 g and the amount of phosphate by 30 g.

To the composition is added oil of peppermint 1 g. The viscosity is found to be about 3900 cp. The solution is dispensed as in Example 1 so that the given dose is either 5 mg or 2.5 nicotine.

Example 4

The procedure set forth in Example 1 is followed, but the amount of nicotine is replaced by 100 g, the phosphate is excluded, and the pH is adjusted to 2.

To the composition is added oil of wintergreen 1 g and butylated hydroxyanisole 0.1 g. The viscosity is found to be about 3600 cp. The solution is dispensed as in Example 1 so that the given dose is 5 mg nicotine.

Example 5

The procedure set forth in Example 1 is followed, but the amount of nicotine is replaced by 20 g and the sodium dihydrogen phosphate by sodium monohydrogen phosphate, Na_2HPO_4, $2H_2O$, 10 g.

The viscosity is found to be about 3900 cp.

The solution is dispensed as in Example 1 so that the given dose is either 2 mg or 1 mg nicotine.

Example 6

The procedure set forth in Example 1 is followed, but the addition of phosphate is excluded. The viscosity is found to be about 4000 cp. The solution is dispensed as in Example 5.

Example 7

The procedure set forth in Example 1 is followed, but the addition of phosphate is excluded, the pH adjusted to about 5, sodium bisulfite 1 g added as an antioxidant, sodium benzoate 1 g as a preservative, and vanilla 1 g as a flavouring agent.

The viscosity is found to be about 4000 cp.

The solution is dispensed as in Example 5.

Example 8

The procedure set forth in Example 1 is followed, but the amount of hydroxypropyl methylcellulose is replaced by 22 g.

The viscosity of the solution is found to be about 5900 cp. The solution is dispensed as in Example 1.

Example 9

The procedure set forth in Example 1 is followed, but the amount of hydroxypropyl methylcellulose is replaced by 18 g.

The viscosity is found to be about 3000 cp.

The solution is dispensed as in Example 1.

Example 10

The procedure set forth in Example 1 is followed, but the amount of hydroxypropyl methylcellulose is replaced by 16 g.

The viscosity is found to be about 1900 cp.

The solution is dispensed as in Example 1.

Example 11

Th procedure set forth in Example 1 is followed, but the amount of hydroxypropyl methylcellulose is replaced by 14 g.

Th viscosity is found to be about 1200 cp.

Th solution is dispensed as in Example 1.

Example 12

The procedure set forth in Example 1 is followed, by the hydroxypropyl methylcellulose is replaced by 20 g of hydroxypropyl cellulose (Klucel MF, TM).

The viscosity is found to be about 4200 cp.

The solution is dispensed as in Example 1.

Example 13

The procedure set forth in Example 1 is followed, but the hydroxypropyl methylcellulose is replaced by poly(ethylene oxide) (Polyox WSR-301, TM) 15 g.

The viscosity is found to be about 3200 cp.

The solution is dispensed as in Example 1.

Example 14

Nicotine	10 g
Sodium dihydrogen phosphate NaH_2PO_4, H_2O	5 g
A mixture of microcrystalline cellulose and sodium carboxymethyl cellulose (Avicel RC 591, TM)	20 g
Sorbic acid	5 g
Hydrochloric acid ad pH 6	
Water to make	1000 ml

Avicel Rc 591, TM is dispersed in 800 ml of water. The dispersion is treated by a colloidal mill, type Collovelox. In the dispersion the nicotine is dissoved together with the phosphate, which is acting as a buffer, and the sorbic acid as a preservative agent.

The pH is adjusted to 6 with 5 N HCl and the volume is made up to 1000 ml with water.

The viscosity of the resulting solution is found to be about 2000 cp.

The solution is dispensed in disposable single dose units or multiple-dose containers, which deliver a given unit dose of either 1 mg or 0.5 mg nicotine.

Example 15

Nicotine	20 g
Sodium dihydrogen phosphate NaH_2PO_4, H_2O	20 g
Sodium carboxymethyl cellulose (Cellugel 3000, TM)	21 g
Hydrochloric acid ad pH 4	
Water to make	1000 ml

The nicotine is dissolved in 900 ml of water together with the phosphate which is acting as a buffer. The sodium carboxymethyl cellulose is added and dissolved by stirring. The pH is adjusted to about 4 with 5N HCl.

The volume is made up to 1000 ml with water. The viscosity is found to be about 1800 cp.

The solution is dispensed in disposable single dose units or multiple-dose containers, which deliver a given unit dose of either 2 mg or 1 mg nicotine.

Example 16

The procedure set forth in Example 15 is followed, but the sodium carboxymethyl cellulose is replaced by 30 g of methyl cellulose (Methocel A4M, TM).

The viscosity is found to be about 4500 cp.

The solution is dispensed as in Example 15.

Example 17

The procedure set forth in Example 15 is followed, but the sodium carboxymethyl cellulos is replaced by 15 g of hydroxyethyl cellulose (Cellosize QP 4400, TM).

The viscosity is found t be about 3500 cp.

The solution is dispensed as in Example 15.

Example 18

Nicotine ..... 20 g

Tartaric acid (natural acid) ..... 15 g

Hydroxypropyl methylcellulose
(Methocel E4M, TM) ..... 20 g

Water to make ..... 1000 ml

The nicotine is dissoved in 500 ml of water together with the tartaric acid.

The hydroxypropyl methylcellulose is dispersed in 300 ml of water at about 60°C. The nicotine solution is added with stirring to the warm cellulose slurry and the mixture is allowed to cool.

The volume is made up to 1000 ml with water. The pH of the solution found to be about 4.

The viscosity of the solution is found to be about 3900 cp.

The solution is dispensed in disposable single dose units or multiple-dose containers, which deliver a given unit dose of either 2 mg or 1 mg nicotine.

Example 19

The procedure set forth in Example 18 is followed, but the tartaric acid is replaced by 12.3 g succinic acid.

The pH is found to be about 5.

The viscosity is found to be about 3800 cp.

The solution is dispensed as in Example 18.

Example 20

The procedure set forth in Example 18 is followed, but the tartaric acid is replaced by 26.3 g lactic acid (90%).

The pH is found to be about 4.

The viscosity is found to be about 3900 cp.

The solution is dispensed as in Example 18.

Example 21

The procedure set forth in Example 18 is followed, but the tartaric acid is replaced by 12.9 g citric acid.

The pH is found to be about 5.

The viscosity is found to be about 3800 cp.

The solution is dispensed as in Example 18.

Example 22

The procedure set forth in Example 18 is followed, but the amount of tartaric acid is changed to 25 g.

The pH is adjusted to about 4 with 5N NaOH, which means that in the solution about 10 g of the tartaric acid constitute a buffer.

The viscosity is found to be about 3900 cp.

The solution is dispensed as in Example 18.

Example 23

The procedure set forth in Example 18 is followed, but the tartaric acid is replaced by 32.3 g succinic acid.

The pH is adjusted to about 5 with 5N NaOH, which means that in the solution about 20 g of the succinic acid constitute a buffer.

The viscosity is found to be about 3800 cp.

The solution is dispensed as in Example 18.

Example 24

The procedure set forth in Example 18 is followed, but the tartaric acid is replaced by 56.3 g lactic acid (90%).

The pH is adjusted to about 4 with 5N NaOH, which means that in the solution about 30 g of the lactic acid constitute a buffer.

The viscosity is found to be about 3900 cp.

The solution is dispensed as in Example 18.

Example 25

The procedure set forth in Example 18 is followed, but the tartaric acid is replaced by 42.9 g citric acid.

The pH is adjusted to about 5 with 5N NaOH, which means that in the solution about 30 g of the citric acid constitute a buffer.

The viscosity is found to be about 3800 cp.

The solution is dispensed as in Example 18.

Example 26

Nicotine hydrogen (+) tartrate, $C_{10}H_{14}N_2(C_4H_6O_6)_2$, $2H_2O$ (corresponding to 20 g nicotine base) ..... 61.44 g

Hydroxypropyl methylcellulose (Methocel E4M, TM) ..... 20 g

Water to make 1000 ml

The nicotine salt is dissolved in 500 ml of the water.

The hydroxypropyl methylcellulose is dispensed in 300 ml of water at about 60°C. The nicotine solution is added with stirring to the warm cellulose slurry, the mixture is allowed to cool, and the volume is made up to 1000 ml with water.

The pH of the solution is found to be about 3 and the viscosity to be about 3700 cp.

The solution is dispensed in disposable single dose units or multiple-dose containers, which deliver a given unit dose of either 2 mg or 1 mg nicotine.

Example 27

The procedure set forth in Example 26 is followed, but the nicotine hydrogen (+) tartrate is replaced by 42.96 g of nicotine (+) tartrate, $C_{10}H_{14}N_2$, $C_4H_6O_6$, $2H_2O$, corresponding to 20 g nicotine base.

The pH of the solution is adjusted to about 4 with tartaric acid.

Its viscosity is found to be about 3900 cp.

The solution is dispensed as in Example 26.

Example 28

The procedure set forth in Example 26 is followed, but the nicotine hydrogen (+) tartrate is replaced by 24.5 g nicotine hydrochloride, $C_{10}H_{14}N_2$, HCl, corresponding to 20 g nicotine base.

The pH of the solution is adjusted to about 4 with 5N HCl.

Its viscosity is found to be about 3900 cp.

The solution is dispensed as in Example 26

Example 29

The procedure set forth in Example 26 is followed, but the nicotine hydrogen (+) tartrate is replaced by 29 g nicotine dihydrochloride, $C_{10}H_{14}N_2$, 2HCl, corresponding to 20 g nicotine base.

The pH of the solution is about 3.

Its viscosity is found to be about 3700 cp.

The solution is dispensed as in Example 26.

Example 30

The procedure set forth in Example 26 is followed, but the nicotine hydrogen (+) tartrate is replaced by 52.1 g nicotine sulphate, $(C_{10}H_{14}N_2)_2$, H_2SO_4, corresponding to 20 g nicotine base.

The pH of the solution is about 3.

Its viscosity is found to be about 3700 cp.

The solution is dispensed as in Example 26.

Example 31

Nicotine ..... 20 g

Sodium dihydrogen phosphate, NaH_2PO_4, H_2O 15g

Water ..... ad 785 g

Pretrolatum ..... 42.5 g

White wax ..... 30 g

Lanolin anhydride 22.5g

Sorbitan sesquioleate (Arlacel 83, TM) ..... 20 g

Mineral oil ..... 100 g

The first four components are mixed; the resultant aqueous solution is heated to about 70°C. The last five components are melted togeth r and mixed at about 70°C. The second mixture is added to the first with continuous agitation and c oling to r om temperature.

The viscosity of the resulting w/o-emulsion is f und to be 1400 cp. It is dispensed in disposable single dose units or multiple-dose containers which deliver a given unit dose of eith r 2 mg or 1 mg nicotine.

Example 32

Nicotine ..... 20 g

Tartaric acid ..... 25 g

5N NaOH ad pH 4

Propylene glycol ..... 10 g

Sorbitol 70% ..... 40 g

Water ..... ad 710 g

Mineral oil ..... 170 g

Isopropyl myristate ..... 50 g

White wax ..... 10 g

Polyoxyethylene sorbitan trioleate (Tween 85, TM) ..... 30 g

Sorbitan sesquioleate (Arlacel 83, TM) ..... 30 g

The first six components are mixed; the resultant aqueous solution (in which about 10 g or the tartaric acid constitute a buffer) is heated to 70°C. The last five components are melted together and mixed at 70°C. The second mixture is added to the first with continuous agitation and cooling to room temperature.

The viscosity of the resulting o/w-emulsion is found to be about 2200 cp.

It is dispensed in disposable single dose units or multiple-dose containers, which deliver a given unit dose of either 2 mg or 1 mg nicotine.

Example 33

Nicotine ..... 10 g

Tartaric acid (natural acid) ..... 10 g

Polyethylene glycol 4000 100 g

Hydroxyethyl cellulose (Cellosize QP 4400) ..... 17 g

Sorbic acid ..... 1 g

Flavouring mixture ..... 0.6 g

Water to make 1000 ml

pH adjusted to 5 with sodium hydroxide

The nicotine is dissolved in 500 ml of water together with the tartaric acid.

The hydroxyethyl cellulose is dispersed in 300 ml of water at about 60°C. The nicotine solution is added with stirring to the warm cellulose slurry and the mixture is allowed to cool.

Administration and Pharmacology

The administration of a composition of the invention to a subject as a substitute for smoking comprises the step of applying to the nasal mucosa in the nasal cavity of the subject a composition according to the invention. This is effected without difficulty. The subject simply maintains his head in an upright position, in preference to a backwardly-tilted position, to avoid unnecessary entry of the composition into the buccal cavity through the rear of the nasal passageway. Upon exerting pressure upon th pressure-application chamber of a unit-dose container in which th compositi n of the invention is contained, preferably in the nasally-insertabl neck thereof, the unit-dose is conveniently expelled into the nasal passageway and into contact with the nasal mucosa. Of course, when the comp sition is so packaged, th unit-dose contain r is usually initially closed by a small plastic appendage which must be removed prior to administration, as is normal in th art. When th composition of the invention is packaged in a multi-d se container having a unit-dose neck, the same procedure is employed. Of course, ther ways of administration may be utilized, such as th employment of a dropper, syringe, or the like, but administration in a unit-dose container according to th foregoing description constitutes a preferred mode of packaging and operation according t

the invention. After waiting a short time, generally less than ten minutes, the blood levels of the subject will rise substantially and the nicotine content, after administration of a 2 mg nicotine single unit dose, will attain a level between 10 and 20 ng, about equivalent to the blood levels obtained upon smoking a normal cigarette (see O. Fernö in World Smoking & Health *5* (1980) 24-29). Substantial or habitual smokers experience a feeling of smoking satisfaction upon administration of a composition of the invention and, of course, administration to subjects in need of such administration or desiring the same is accomplished with facility, even though they may be denture wearers.

Proceeding according to the method of administration of the present invention, any of the compositions of the foregoing examples may be employed. They are found to be well tolerated, particularly at the lower pH-levels and, especially when a buffering agent is present therein, even at higher pH-levels. The viscosity maintains the composition in contact with the nasal mucosa for an adequate period for absorption to occur.

Representative tests upon substantial or habitual smoking subjects were carried out employing compositions of the foregoing examples.

In such a test upon occasional cigar smokers using compositions of the foregoing examples, namely, of examples 5 and 6, the following blood levels were obtained upon administration to the nasal mucosa of the two subjects involved in a single unit dose of 2 mg nicotine (0.1 ml).

Time after administration of the composition in minutes	Blood level of nicotine (ng/ml) found with 2 mg nicotine of the composition of Example 6 Subject 1	Example 5 Subject 2
1	1.0	1.3
2.5	7.3	2.4
5	16.0	4.1
7.5	14.7	8.5
10	14.4	15.8
15	11.1	13.1
20	9.8	10.3
30	7.3	7.7
45	7.2	6.1
60	5.8	4.9

The blood levels of nicotine before the experiment started were below 1 ng/ml in both subjects.

As seen from the figures above an effective blood level of approximately 16 ng/ml of nicotine was obtained within 5 and 10 minutes, respectively, and the blood levels of both of the subjects involved evidence that the compositions of the invention do in fact provide nicotine blood levels approximately equivalent to those obtained upon the smoking of a normal cigarette. In both cases, the subjects not only experienced the elevated nicotine blood levels, but found it possible to abstain from smoking during an extended period after administration.

CLAIMS

1. An aqueous composition having a viscosity of at least 100 cp and pH of from 2 to 6, which contains 0.5 to 10 % w/v, calculated as a free base, of nicotine or a physiologically-acceptable acid addition salt thereof.
2. A composition according to claim 1, which has a pH of from 3 to 5.
3. A composition according to claim 1 or claim 2, which comprises a buffer.
4. A composition according to claim 3, which is buffered at a pH of from 4 to 6.
5. A composition according to any preceding claim, which contains from 1 to 5 % w/v of nicotine.
6. A composition according to claim 5, which comprises from 2 to 4 % w/v of nicotine.
7. A composition according to any preceding claim, which comprises a thickening agent which is natural or synthetic polymer.
8. A composition according to any preceding claim, which comprises an emulsified oil phase.
9. A composition according to any preceding claim, which comprises an emulsifying agent.
10. A compositi n according to any preceding claim, which has a viscosity of from 1000 to 6000 cp.
11. A composition according to claim 10, which has a viscosity of from 3000 to 4000 cp.
12. A composition according to any preceding claim, which comprises a preservative.
13. A composition according to any preceding claim, which comprises a flavouring agent.
14. A composition according to any preceding claim, which c mprises an anti-oxidant.
15. A composition according to any preceding claim, in the form of a unit dosage having a volume of from 0.05 t 0.5 ml.
16. A composition according to claim 15, in which the unit dosage has a volume of from 0.1 to 0.3 ml.
17. A composition according to claim 1, substantially as illustrated in any of the Examples.

18. A composition according to any preceding claim, for nasal administration.

19. A composition according to any preceding claim, for use in reducing tobacco-dependence.

20. A squeezable container containing a composition according to any preceding claim, in which the container has a neck outwardly adapted for insertion into a nostril and inwardly adapted for insertion into a nostril and inwardly adapted to hold a pre-determined volume of a composition which can be discharged through the neck on squeezing the container.

21. A container according to claim 20, in which the pre-determined volume is such that squeezing the container discharges a unit dosage volume according to any of claims 15 and 16.

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